REMARKS

Entry of the foregoing, reexamination and reconsideration of the above-identified application are respectfully requested.

Claim 31 has been deleted and claim 32 has been amended to be an independent claim. Claims have also been amended to depend from claim 32 rather than claim 31. No new matter has been added by these amendments. Nor have new issues been raised. Entry of these amendments is thus consistent with 37 C.F.R. §1.116.

As a result of the instant amendment, the claims of record now read on the elected invention.

Claims 31-45 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Li et al or Takeda et al taken with "Reg. No. H271" or Whaun et al. This rejection is respectfully traversed.

Li et al teaches injection of harringtonine (HA) and homoharringtonine (HO) in leukemia mice. Takeda et al was said to teach that "HA and HO had significant activates against P388 leukemia, L1210 leukemia ... by i.p. injection." The cited Abstract does not identify humans as being subject to the treatment.

The primary references fail to disclose or even suggest a method of treating leukemia *in humans* using *subcutaneous* mode of administration. Nor do they disclose using the homoharringtonine or harringtonine in the *salt or tautomeric form*, wherein in the formulation, the *pH is between 5.5 and 8.5*, as required by the instant claims.

The secondary references fail to overcome or remedy the deficiencies of the primary references. Reg No. H 271 is said to teach subcutaneous administration of

homoharringtonine. Whaun et al is asserted to show subcutaneous injections at page 234, line 5. However, like the primary references, neither Reg No. H 271 nor Whaun et al disclose or suggest a method of treating leukemia *in humans* using *subcutaneous* mode of administration. Nor do they disclose using the homoharringtonine or harringtonine in the *salt or tautomeric form*, wherein in the formulation, the *pH is between 5.5 and 8.5*, as required by the instant claims. The combination of art thus fails to teach the invention as claimed.

The Official Action asserts that "there is no showing that for treating Leukemia, the subcutaneous injection is better than the prior art injections." Page 2. Such a showing is said to be required "[s]ince harringtonine has been administered by subcutaneous injection." Page 2. It is further asserted that "most injectable composition are at a neutral pH (about 7)." These assertions are in error. It is respectfully submitted that subcutaneous administration was *not* previously shown to be used for human administration.

Regarding the assertion that harringtonine has been administered by subcutaneous injection, this assertion is irrelevant to the invention as claimed. The claims are directed to treatment of leukemia in a *human* patient. There is no showing in the cited art of subcutaneous administration of harringtonines in *humans*. Instead, the only art showing subcutaneous administration of homoharringtonine is Reg No. H 271 and Whaun et al. These references do not show subcutaneous administration in *humans* of harringtonine or homoharringtonine for treatment of leukemia. Instead, Reg No. 271 shows administration in *mice with malaria*. When humans are described as being treated, *continuous infusion* of homoharringtonine was used. Contrary to the assertion in the Official Action, this reference would teach

away from the claimed invention in that it would show that, while one skilled in the art might use subcutaneous administration in mice, it would not have been used in humans prior to the instant invention.

In Whaun, as stated in applicants' prior response, "the method of administration was not reported" for the data obtained showing treatment of leukemia. *See,* page 231, line 1. It cannot simply be assumed that the subcutaneous mode of administration was used. As shown by Reg No. 271, subcutaneous administration of homoharringtonines was not used in humans for treatment of leukemia. While Whaun uses subcutaneous injections in mice, as evidenced by Reg No. 271, it cannot be assumed that the same method of administration was used in humans. The prior art, as shown by Reg. No. H271, would teach away from using subcutaneous administration in humans, even when used in mice.

One skilled in the art would have known that, for a great number of anti-cancer compounds, subcutaneous mode of administration is dangerous when used in humans. The reason is due to local toxicity, such as tissue necrosis. This is true, for example, for the antracyclin series, *i.e.,* toxorubicin, dororubicin and mitroxartrone, of anti-cancer compounds.

Moreover, the use of homoharringtonine by bolus intravenous injection causes cardiac problems, such as hypotension, because of the appearance of a homoharringtonine peak in blood. For this reason, continuous intravenous administration was preferred on human beings as compared to bolus or rapid intravenous injection. *See, for example,* Stewart et al, *Investigational New Drugs* 3:279-86 (1985), and Malamud et al, *AACR Abstracts*, p. 179, Abstract No. 709

(1984), previously submitted. *See also,* specification page 4, lines 3-8. Therefore, at the time of applicants' invention, one skilled in the art would have believed that the subcutaneous route of administration would provoke the appearance of a homoharringtonine peak in blood, and thus also produce the same toxic effect on the heart as the bolus or rapid intravenous injection. This would have led one skilled in the art away from using subcutaneous route of administration in humans, even if used in mice.

As set forth in the specification at page 6, lines 11-17, the prior art use of harringtonines by weekly or more continuous intravenous infusion, as required prior to the instant invention, had many disadvantages. For example, general infections, e.g., frequent septicemia due to direct introduction of germs by catheter systems, need for highly trained personal and hospitalization of patients for the application of the therapy; difficulties of using the drugs at permanent low doses; and difficulties in using such drugs in the case of elderly and younger patients. These disadvantages were overcome by the instant invention, which allowed for the first time subcutaneous administration of harringtonines to patients in need of such treatment.

However, if the prior art problems, *e.g.,* toxic effects of a harringtonine peak in blood when administered, could be solved, the many advantages of using subcutaneous injection as compared to other modes of intravenous administration could be achieved. These same advantages of the claimed method would apply for treating leukemia via subcutaneous injection as compared to prior art injections.

For example, as stated in the specification, advantages of subcutaneous injection of the harringtonine salts of the instant invention over prior art injections include: (i) better bioavailability of the salt than the base form of the prior art alkaloid

harringtonines; (ii) ability to combine harringtonines with other chemotherapeutic agents in the same subcutaneous injection; (iii) ability to provide bolus injections at regular intervals or by continuous subcutaneous infusion; (iv) excellent local tolerance of the drug administered subcutaneously and durability of the therapeutic efficacy expected against leukemias; (v) improved quality of life; (vi) the patient can self inject the product; (vii) reduction in risk of general infections, e.g., risks of septicaemia by the introduction of germs are null; (viii) lower cost to patient, e.g., eliminate additional costs related to existing complex delivery systems such as electronic pump, disposable continuous infusion systems and hospitalization; (ix) overdoses are not possible, and (x) subcutaneous mode of administration allows discontinuous injection which permits the synchronization of the cellular cycle which is beneficial for the therapy (all the cells are in the same multiplication phase). This synchronization is *not* possible, for example, when using continuous intravenous administration. The instant invention thus offers many advantageous and beneficial results, which were *not* expected prior to applicants' findings. *See,* page 7, line 15 - page 8, line 30.

These advantages of the subcutaneous form of injection as instantly claimed are a sufficient showing of why the claimed invention has advantageous and beneficial results over the prior art. These advantages were set forth in our prior response on pages 13-14, but were not addressed in the Official Action.

The Official Action further asserts that "most injectable composition are at a neutral pH (about 7)." This assertion is irrelevant. The general pH of injectable compositions is not relevant to the patentability of the specifically claimed invention. Prior to the instant invention, homoharringtonine compositions used for

administration to humans were acidic and were not neutral. As stated in the specification, "[s]ince 1985 an acidic preparation bearing a pH ranging from 3 to 5.5 has been used for all clinical trails performed under the auspices of NCI." Page 6, lines 5-7. Prior to 1985, "the base form of alkaloid homoharringtonine was used for animal screening and in early studies in humans in the U.S." Page 6, lines 4-5. Thus, the neutral form of harringtonine or homoharringtonine was previously not used for treatment of leukemia in humans. That other injectable compositions are at neutral pH is irrelevant.

The harringtonine used according to the instant invention are specifically adapted formulations prepared from the salts forms, wherein the pH range of the formulation is between 5.5 and 8.5, *i.e.,* a neutral pH (*see, e.g.,* page 7, lines 9-14 of the specification). On the contrary, in all the cited references, the HHT being used is either the base form, or the salt form in a solution with a pH of less than 5.5. As set forth in the specification, the salt form of the harringtonines "had much better bioavailability than the base form of the alkaloids harringtonines used in early clinical trials." Page 7, lines 16-19.

The combination of cited references thus fails to disclose or even suggest the invention as claimed. The choice of this particular pH range leads to a compromise between the stability of the salt form of HHT (pK=3.5) and the tolerance of the product. As shown in Fig. 1 of the instant application, the formulation as recited in the instant claims has better bioavailability than the base form, as used in the cited art. Fig. 2 illustrates the good tolerance of this formulation, upon administration, as compared to the base form.

Such improved results upon subcutaneous administration of the base form at neutral pH is neither taught nor suggested by the prior art. The instant application thus shows unexpected results of the instant invention.

The combination of references, as set forth above, thus fails to disclose or suggest the invention as claimed.

In view of the above, withdrawal of this rejection of record is respectfully requested. Such action is believed to be in order.

Claims 31, 33-41 and 43-45 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. In claims 31, 33-41 and 43-45, the terms "Q^1" and "R^7" are said not to be defined. This rejection is rendered moot by the instant amendment. Claim 31 and 41 have been deleted, and the remaining claims subject to this rejection have been amended to depend from claim 32. Claim 32 (as well as claim 42) was not subject to this rejection.

In view of the above, withdrawal of this rejection of record is respectfully requested and believed to be in order.

It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, a Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (703) 836-6620 so that prosecution of the application may be expedited.

Respectfully submitted,

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